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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/822,716	03/30/2001	David A. Edwards	2685.1003-008	7248

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EXAMINER	
HAGHIGHATIAN, MINA	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/822,716	EDWARDS ET AL.	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the amendments and response filed 10/27/03. Claims 1-52 are pending.

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Applicant's arguments, filed 10/27/03, with respect to the rejection(s)of claim(s) 1-52 under 35 USC 103 (over Jensen et al in view of the comments) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made. See below.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7, 11-17, 21-26, 28, 49 and 51 are rejected under 35 U.S.C. 102(e) as being anticipated by Jensen et al (6,043,214).

Jensen et al teach method for producing powder formulation comprising an insulin. Jensen discloses that administration of insulin via the pulmonary route can be accomplished by either an aqueous solution or a powder preparation. Regarding the stability of proteins, Jensen discloses that so far all powder formulations have been described as mainly amorphous. It has been found that when insulin is combined with as appropriate absorption enhancer and is introduced into the lower respiratory tract in the form of a powder of appropriate particle size, it readily enters the systemic

circulation by absorption through the layer of epithelial cells in the lower respiratory tract (col. 1, lines 51-67).

Jensen et al teach a dry powder composition comprising insulin or an analogue or derivative thereof, an enhancer and zinc (col. 2, lines 40-64). Jensen discloses that the enhancer can be a phospholipid such as lysophosphatidylcholine (col. 3, lines 1-8).

The compositions of Jensen generally are said to include between 2 and 12 Zn atoms per insulin hexamer (col. 3, lines 40-48). Examples I, III and IV include a 4% Zinc chloride solution. Jensen also discloses that the preferred analogues of insulin are the ones that include amino acids such as alanine, leucine, valine, etc (col. 2, lines 23-27; col. 3, lines 13-17). Jensen et al teach that the size of the particles is between 1 and 5 microns (col. 4, line 46-47). The formulations of Jensen are said to optionally include a carrier or excipient generally accepted for pulmonary administration (col. 4, lines 9-14)

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-10, 12-17, 21-26, 28, 49 and 51-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (6,043,214) in view of Maa et al (6,284,282 B1).

Jensen et al, discussed above, lacks specific disclosure on tap density of the powder particles.

Maa et al discloses a method of spray freeze drying proteins for pharmaceutical administration. The said dry powder compositions comprising particles of a protein of a mean diameter of less than 5 micron (col. 2, lines 10-20). The protein particles are also said to have a tap density of less than about 0.8 g/cm^3, with a tap density of less than about 0.4 g/cm^3 being preferred and less than about 0.1 g/cm^3 being especially preferred (col. 6, lines 5-12). Maa et al discloses proteins which include insulin (col. 6, line 46).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made given the general teachings of a powder formulation of insulin of Jensen et al, to have looked in the art for specific particle characteristics such as tap density, as disclosed by Maa et al, with the reasonable expectations of preparing effective formulations for pulmonary delivery by improving their dispersibility, absorbability and respirability.

Claims 1-17, 21-28, 30-40, 44-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (6,043,214) in view of Weers et al (6,309,623 B1).

Jensen et al, discussed above, lacks specific disclosure on tap density and geometric diameter of the insulin particles.

Weers et al teach stabilized preparations for the delivery of a bioactive agent to the respiratory tract of a patient using a metered dose inhaler. The particles are said to

have a mean geometric diameter of less than 20 micrometer or less than 10 micrometer, and most preferably less than about 5 micrometer (col. 13, lines 34-45).

Weers teaches the particles to have a tap density of less than 0.5 g/cm^3 and most often less than about 0.1 g/cm^3 (col. 14, lines 28-31). The mean aerodynamic diameter of the particles is less tan about 3 micrometer. Said particle distributions will act to increase the deep lung deposition of the administered agent (col. 14, lines 38-43). Weers also discloses that the said inhalation formulations contain active agents such as proteins and peptide including insulin (col. 19, lines 50-54; col. 20, line 6).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made given the general teachings of a powder formulation of insulin of Jensen et al, to have looked in the art for specific particle characteristics such as tap density, as disclosed by Maa et al, with the reasonable expectations of preparing effective formulations for pulmonary delivery by improving their dispersability, absorbability and respirability.

Claims 18-20, 29 and 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (6,043,214) in view of International Ingredient Dictionary and Handbook.

Jensen et al, discussed above, lacks specific disclosure on the inclusion of carboxylic acid in the formulation. However Jensen teaches that hydrochloric acid is added to the formulations to adjust the pH. On the other hand, International Ingredient

Dictionary and Handbook discloses that carboxylic acids such as citric acids are well known pH adjusters in pharmaceutical and cosmetic formulations. Therefore, one of ordinary skill in the art would have been motivated to replace hydrochloric acid of Jensen with citric acid to perform a pH adjusting function. The expected result would be a successful formulation for the pulmonary delivery of insulin.

Response to Arguments

Applicant's arguments filed 10/27/03 regarding the Jensen et al reference have been fully considered but they are not persuasive.

Applicant argues that Jensen et al does not teach delivery to the pulmonary system and does not teach the release of the agents to be sustained. This is incorrect. Jensen specifically teaches "administration of insulin via the pulmonary route" and "the delivery of insulin powders to the lower respiratory tract" (see e.g. col. 1, lines 46, 52, 63-64; col. 2, lines 18 and 45). Applicant continues this argument by stating that "Jensen deftly avoids all reference to pulmonary delivery, except for the Background section and his own definition of enhancer". Examiner disagrees with the said statement because 1) presence of a disclosure in the background section or in the definition does not negate its disclosure. 2) Jensen has this assertion in his Description of the invention section too (please see col. 2, line 45). It also should be noted that in his definition of an enhancer, Jensen is specifically disclosing that the purpose of the enhancer is to make the insulin better absorbed through the layer of epithelial cells lining the alveoli of the lung.

Applicant argues that Jensen does not teach "sustained release". This is not persuasive because the limitation of "sustained release" is considered a property rather than a method step or a component.

Remaining arguments are moot in view of the new rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 571-272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mina Haghighatian
February 12, 2004

MICHAEL G. HARTLEY
PRIMARY EXAMINER

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